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Applicant	:	David R. Hennings et al.		
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Title	:	Endovenous Closure of Varicose Veins with Mid Infrared Laser		
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Mail Stop AMENDMENT
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAMES W. GERIAK

I, James W. Geriak, do declare and say as follows:

1. I am one of the inventors named in the above-identified application.

2. Attached hereto as Exhibit A is a true and correct copy of *Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results*, by Robert J. Min, MD et al., JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY, August 2003.

3. Attached hereto as Exhibit B is a true and correct copy of *Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood*, by T.M. Proebstle, MD et al., DERMATOLOGIC SURGERY, July 2002.

CERTIFICATE OF MAILING (37 CFR §1.8)

I hereby certify, pursuant to 37 CFR §1.8, that I have reasonable basis to expect that that this paper or fee (along with any referred to as being attached or enclosed) would be mailed or transmitted on or before the date indicated with the United States Postal Service with sufficient postage as first class mail on the date shown below in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Dated: November 22, 2005

Sally Hartwell

DOCSOC1:169185.1

4. Attached hereto as Exhibit C is a true and correct copy of *Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: Thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles*, by T.M. Proebstle, MD et al., JOURNAL OF VASCULAR SURGERY, April 2002.

Further, Declarant sayeth not:

I declare under penalty of perjury that the foregoing is true and correct. Executed this 22 day of November 2005 at Irvine, California.

James W. Geriak

Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results

Robert J. Min, MD, Neil Khilnani, MD, and Steven E. Zimmet, MD

PURPOSE: To report long-term follow-up results of endovenous laser treatment for great saphenous vein (GSV) reflux caused by saphenofemoral junction (SFJ) incompetence.

MATERIALS AND METHODS: Four hundred ninety-nine GSVs in 423 subjects with varicose veins were treated over a 3-year period with 810-nm diode laser energy delivered percutaneously into the GSV via a 600-μm fiber. Tumescent anesthesia (100–200 mL of 0.2% lidocaine) was delivered perivenously under ultrasound (US) guidance. Patients were evaluated clinically and with duplex US at 1 week, 1 month, 3 months, 6 months, 1 year, and yearly thereafter to assess treatment efficacy and adverse reactions. Compression sclerotherapy was performed in nearly all patients at follow-up for treatment of associated tributary varicose veins and secondary telangiectasia.

RESULTS: Successful occlusion of the GSV, defined as absence of flow on color Doppler imaging, was noted in 490 of 499 GSVs (98.2%) after initial treatment. One hundred thirteen of 121 limbs (93.4%) followed for 2 years have remained closed, with the treated portions of the GSVs not visible on duplex imaging. Of note, all recurrences have occurred before 9 months, with the majority noted before 3 months. Bruising was noted in 24% of patients and tightness along the course of the treated vein was present in 90% of limbs. There have been no skin burns, paresthesias, or cases of deep vein thrombosis.

CONCLUSIONS: Long-term results available in 499 limbs treated with endovenous laser demonstrate a recurrence rate of less than 7% at 2-year follow-up. These results are comparable or superior to those reported for the other options available for treatment of GSV reflux, including surgery, US-guided sclerotherapy, and radiofrequency ablation. Endovenous laser appears to offer these benefits with lower rates of complication and avoidance of general anesthesia.

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Abbreviations: GSV = great saphenous vein, RF = radiofrequency, SFJ = saphenofemoral junction

LOWER-extremity venous insufficiency is a common medical condition afflicting 25% of women and 15% of men in the United States (1). Gender, pregnancy, hormones, aging, and gravitational forces from prolonged standing or sitting are the most common factors that influence the appearance or worsening of primary varicose veins (2,3). Although many people seek medical treatment for varicose veins because they find them unsightly, most people with varicose veins do experience symptoms (4,5). Unfortunately, symptoms of primary venous insufficiency are often not recognized by patients or their physicians. Characteristic leg complaints associated with varicose veins include aching pain, night cramps, fatigue, heaviness, or restlessness. Symptoms arise from pressure on somatic nerves by dilated veins and are typically worsened with prolonged standing, during the premenstrual period, or in warm weather (6). Left untreated, nearly 50% of patients with significant superficial venous insufficiency will eventually experience chronic venous insufficiency characterized by lower-extremity swelling, eczema, pigmentation, hemorrhage, and ulceration (7).

Great saphenous vein (GSV) reflux is the most common underlying cause of significant varicose veins. Traditional treatment of GSV reflux has been surgical removal of the GSV. Al-

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R.J.M. is a consultant to Diomed (Andover, MA), assisting in development of medical treatments and physician training. R.J.M. is coinventor and part owner of a patent on endovenous laser treatment of veins, for which he receives royalties. R.J.M. and Cornell Vascular have paid for all medical equipment used in procedures relating to this study. S.E.Z. is a paid consultant to Diomed, Inc. (Andover, MA), assisting in development of medical treatments. S.E.Z. is also paid to assist in physican training. S.E.Z. purchased all medical equipment he used in connection with this study. The other author has not identified a potential conflict of interest.

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though surgical ligation and stripping of the GSV has been the most durable treatment, it is associated with significant perioperative morbidity. Less-invasive surgical treatments including high ligation of the GSV at the saphenofemoral junction (SFJ) have been attempted with the hope that gravitational reflux would be controlled while the vein is preserved for possible use as a bypass graft. Unfortunately, ligation of the GSV alone usually results in recurrent varicose veins (8). Even when high ligation has been combined with phlebectomy of varicose tributaries or retrograde sclerotherapy, recurrence has been the rule (9,10). Therefore, when it is determined that GSV reflux is the principal underlying problem, treatment should involve eliminating this source of reflux with ablation of any associated incompetent venous segments.

In 1999, Boné (11) first reported on delivery of endoluminal laser energy. Since then, a method for treating the entire incompetent GSV segment has been described (12,13). Endovenous laser treatment, which received approval from the US Food and Drug Administration in January 2002, allows delivery of laser energy directly into the blood vessel lumen. Nonthrombotic vein occlusion is accomplished by heating the vein wall with 810-nm-wavelength laser energy delivered via a 600-μm laser fiber (Diomed, Andover, MA). Sufficient heating of the vein wall is necessary to cause collagen contraction and denudation of endothelium. This stimulates vein wall thickening, eventual luminal contraction, and fibrosis of the vein. The purpose of this study is to report on the long-term follow-up results of endovenous laser treatment for GSV reflux.

MATERIALS AND METHODS

This prospective, nonrandomized, consecutive-enrollment study included 423 patients who underwent endovenous laser treatment of incompetent GSV segments with 810-nm diode laser energy delivered intraluminally for treatment of primary varicose veins. The study protocol was approved by the Weill Medical College of Cornell University Institutional Review Board. All patients gave written informed consent before treatment.

Patient Selection

Directed history and physical examination, including duplex ultrasound (US) evaluation of the superficial venous system, was performed on limbs of subjects with varicose veins. Study inclusion criteria included varicose veins caused by SFJ incompetence with GSV reflux as demonstrated by duplex US imaging, age of at least 18 years, and ability to return for scheduled follow-up examinations for 12 months after endovenous laser treatment. Exclusion criteria included nonpalpable pedal pulses; inability to ambulate; deep vein thrombosis; general poor health; pregnancy, nursing, or plans to become pregnant during the course of participation in the investigation; and extremely tortuous GSVs that would not allow endovenous catheterization and passage of the laser fiber as identified on pretreatment venous duplex US mapping. After initial consultation and evaluation, subjects meeting the appropriate criteria were offered surgery versus endovenous laser treatment. Nearly all subjects chose endovenous laser over surgical ligation and stripping.

Five hundred four incompetent GSVs were treated with endovenous laser over a 39-month period. Five limbs were lost to follow-up. The remaining 499 limbs in 423 patients comprise the study population. This group consists of 352 women (83%) and 71 men (17%) ranging in age from 23 to 72 years, with a mean age of 42 years.

Follow-up ranged from 1 month to 39 months with a mean follow-up period of 17 months and an SD of 11 months. Aching leg pain was the most common presenting symptom, found in 87% of limbs. Overall, slightly more left legs (n = 263, 53%) were treated, and 76 patients (18%) were treated for bilateral GSV reflux. Pretreatment GSV diameter, measured in the upright position approximately 2 cm below the SFJ, ranged from 4.4 mm to 29 mm (mean, 11 mm; SD, 4.2 mm).

None of the patients in this series underwent concomitant ambulatory phlebectomy. All but seven patients underwent compression sclerotherapy treatment of distal varicose tributaries or associated telangiectasias at follow-up visits.

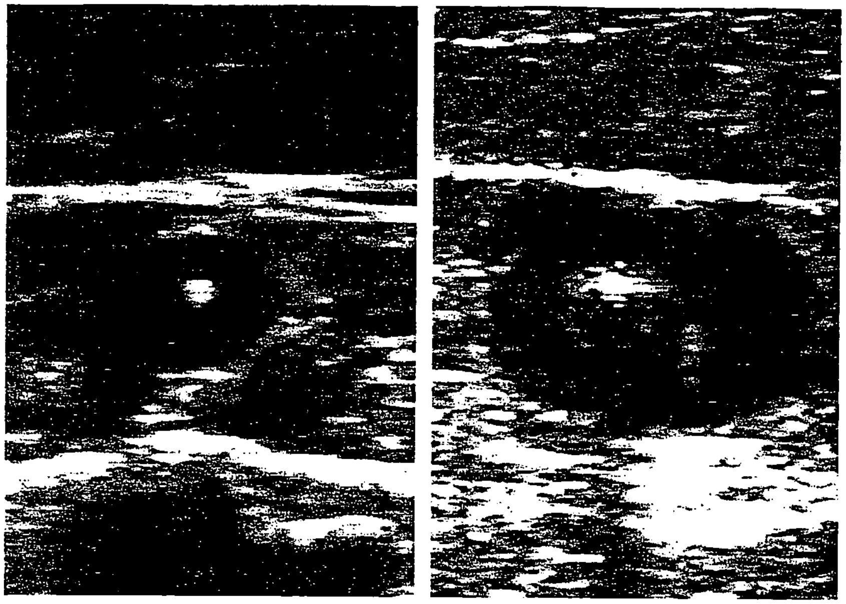
Description of Technique

Duplex US was performed in the upright position to map incompetent sources of venous reflux and then to mark the skin overlying the incompetent portion of the GSV starting at the SFJ. After venous duplex mapping, a percutaneous entry point was chosen. This point may be where reflux is no longer seen or where the GSV becomes too small to access (usually just above or below knee level). With use of local anesthesia and sonographic guidance, the GSV was punctured. A 5-F introducer sheath was placed into the GSV over a guide wire and advanced past the SFJ into the femoral vein. Intraluminal position within the GSV was confirmed by aspiration of nonpulsatile venous blood and visualization with US.

The sheath was flushed and a 600-μm laser fiber (Diomed) was inserted in the sheath and advanced up to the first site mark, indicating that the distal tip of the laser fiber was flush with the end of the sheath. The sheath was then withdrawn to the second site mark, exposing the distal 3 cm of the bare-tipped laser fiber. The sheath and fiber were pulled back together and positioned at the SFJ under US guidance. Position was confirmed by direct visualization of the red aiming beam of the laser fiber through the skin.

Tumescent local anesthesia consisting of 100–200 mL of 0.2% lidocaine neutralized with sodium bicarbonate, was administered along the perivenous space with use of US guidance. In addition to the anesthetic effects, properly delivered, this fluid serves two important functions: (1) it compresses and reduces the diameter of even the largest veins to provide vein wall apposition around the fiber tip with subsequent circumferential heating of the vein wall and (2) it provides a "heat sink" to minimize the possibility of heat-related damage to adjacent tissues. **Figure 1a** demonstrates the typical transverse sonographic appearance of the laser fiber and catheter seen centrally within an enlarged GSV located in the saphenous space. Proper and adequate delivery of tumescent anesthesia should result in fluid surrounding a compressed GSV as shown in **Figure 1b**.

The tip of the laser fiber was repo-



a. b.

Figure 1. Duplex US (transverse view) demonstrating appearance of the GSV before and after proper delivery of tumescent anesthesia. (a) Intraluminal position of laser fiber and catheter within an enlarged GSV; (b) tumescent anesthesia delivered by echogenic needle tip adjacent to laser fiber and catheter with fluid surrounding the compressed GSV.

sitioned within the GSV 5–10 mm distal to the SFJ. Tip position was checked by US and direct visualization of the red aiming beam through the skin. Laser energy (810-nm diode laser; Diomed) was delivered at 14 W in continuous mode. The vein was treated from 5–10 mm below the SFJ to approximately 1 cm above the skin entry site. Length of GSV treated with endovenous laser ranged from 10 cm to 55 cm (mean, 35 cm; SD, 10 cm). The laser fiber was withdrawn at an average rate of 3 mm per second (18 cm per minute). Of patients treated with 14-W continuous mode (n = 276, or 55% of limbs), delivery of laser energy ranged from 25 seconds (at 358 J) to 187 seconds (at 2,615 J), with a mean of 123 seconds (SD, 47 sec) or 1,727 J (SD, 650 J).

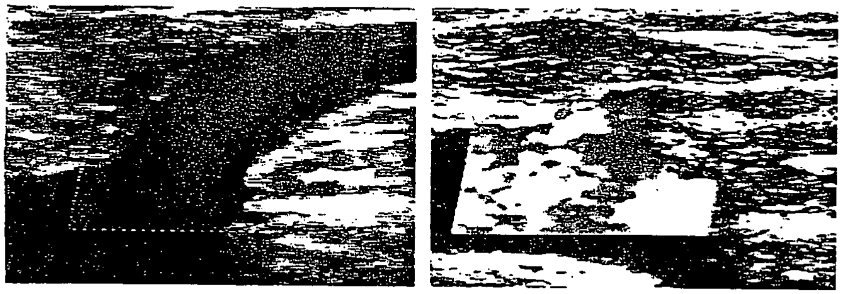
A class II (30–40 mm Hg) full-thigh graduated support stocking or panty hose was worn for at least 1 week at all times except to sleep or to shower. Patients were instructed to ambulate and resume their normal daily activities immediately. Clinical and duplex US follow-up was obtained at 1 week, 1, 3, 6, 9, and 12 months, and then yearly.

Compression sclerotherapy treatment of distal varicose tributaries was performed with use of sodium tetradecyl sulfate (0.3%–1% concentration). A detailed description of sclerotherapy technique is beyond the scope of this article but the approach used was the "French school" originally advocated by Tournay and more recently popularized in the United States by Goldman and other phlebologists (14). This technique relies on starting from the highest points of reflux and proceeding downward, and treating veins from the largest to the smallest. Compression stockings or panty hose were worn for at least 1 week after sclerotherapy treatments except to sleep or shower. Sclerotherapy treatments were performed at 4-week intervals, starting 1 month after endovenous laser ablation of the GSV.

Study Endpoints and Definitions

Duplex US criteria for successful treatment were the following: at 1-week follow-up, an enlarged noncompressible GSV, minimally decreased in diameter, with echogenic, thickened vein walls, and no flow seen within the occluded vein lumen on color Doppler interrogation; at 3- and 6-month follow-up, an occluded GSV with substantial (>50%) reduction in diameter; and at 1 year and beyond, complete disappearance of the GSV or minimal residual fibrous cord with no flow detectable. It is important to note that the expected appearance 1–2 weeks after endovenous laser is a slightly smaller GSV demonstrating wall thickening with absence of flow within the treated vein segment. The vein lumen is usually obliterated by the thickened wall, which has low-level echoes and is incompressible. This wall thickening should be differentiated from acute GSV thrombosis wherein the vein is also incompressible but the lumen is filled with anechoic acute thrombus. Several weeks after successful endovenous laser treatment, resolution of the acute inflammation in the vein wall should result in reduction in vein diameter. After several months, most of the treated vein segments will fibrose and be difficult to identify. Alternatively, superficial thrombophlebitis with GSV thrombus would result in recanalization of the vein. A longitudinal view of an enlarged, incompetent GSV is seen in **Figure 2a. Figure 2b** demonstrates the typical color Doppler appearance of a successfully treated GSV 1 year after endovenous laser treatment.

Clinical evaluation was performed on all subjects at 1 week, 1, 3, 6, 9, and 12 months, and yearly thereafter by the same physician (R.M.) who performed all the endovenous laser procedures. Patients were queried about symptomatic relief at follow-up visits, particularly improvement or resolution of lower-extremity pain believed to be associated with venous insufficiency. Improvement in the appearance of the leg, including reduction in visible varicosities, swelling, pigmentation, or other skin changes secondary to chronic venous insufficiency, were assessed by the patient and with direct comparison with pretreatment photographs obtained from all subjects undergoing treatment. Patients were evaluated for possible adverse reactions caused by endovenous laser treatment at each follow-up visit. Minor complications were defined as those that had no significant clinical sequelae, such as bruising. Major complications were defined as those necessitating an increased level of care, sur-



a. b.

Figure 2. Color Doppler examinations (longitudinal views) of the GSV at the SFJ demonstrating successful occlusion after endovenous laser treatment. (a) Pretreatment evaluation demonstrates an enlarged GSV with reflux after distal calf compression; (b) 1-year follow-up examination shows typical "cul-de-sac" appearance of the proximal GSV with occlusion of the treated segment.

gery, hospitalization, or permanent adverse sequelae.

RESULTS

Follow-up results ranging from 1 month to 39 months (mean, 17 months; SD, 11 months) were obtained in 499 of the 504 limbs treated with endovenous laser during the study period. Successful endovenous laser treatment, as defined earlier, was seen in 490 of 499 limbs (98%) at 1-month follow-up. Eight of nine GSVs requiring repeat endovenous laser were successfully closed with a second endovenous laser treatment. Continued closure of the treated GSV segments was noted at longitudinal follow-up at the following rates: 444 of 447 (99.3%) at 3 months, 390 of 396 (98.5%) at 6 months, 351 of 359 (97.8%) at 9 months, 310 of 318 (97.5%) at 1 year, and 113 of 121 (93.4%) at 2 years. Forty subjects have been followed for 3 years and no new recurrences were seen at 2 or 3 years that were not present at 1-year follow-up. In fact, all recurrences were noted before 9 months, with the majority seen by 3 months. This may indicate that these were not true recurrences but rather inadequate initial treatments.

Clinical examination correlated well with duplex US findings. All patients showed improvement in the appearance of the limb with disappearance or reduction in the size and number of visible varicosities. The typical appearance of varicose veins caused by incompetence of the SFJ with GSV reflux is shown in Figure 3a. One month after endovenous laser treatment, relief of symptoms and significant improvement in the appearance of the varicose veins was noted (Fig 3b). By 6 months after initial treatment, pain was greatly improved or resolved in all treated limbs. Although symptomatic resolution and significant improvement in the appearance of the leg is usually noted after endovenous laser treatment alone, most patients will need additional complementary procedures (ie, sclerotherapy or phlebectomy) to fully realize the restorative benefits of treatment.

Bruising outside the puncture site was noted in 24% of limbs at 1-week follow-up. Bruising resolved in all subjects before 1-month follow-up. Ninety percent of subjects felt a delayed tightness peaking 4–7 days after laser treatment and lasting 3–10 days. This sensation, described as "pulling" along the course of the treated GSV, was not felt in the nine patients in whom initial treatment failed. Five percent of patients developed superficial phlebitis of varicose tributaries after endovenous laser occlusion of the GSV. Most cases required no treatment. Symptomatic patients were treated with graduated compression stockings and over-the-counter antiinflammatory agents. All minor complications listed earlier resolved without sequelae. There have been no skin burns, paresthesias, cases of deep vein thrombosis, or other minor or major complications. The procedure was well-tolerated by all subjects with strictly local anesthesia.

Overall treatment satisfaction was determined by asking subjects if they would recommend the procedure to a friend with similar leg vein problems, and 422 of 423 subjects (99.8%) indicated they would recommend the procedure.

DISCUSSION

Percutaneous methods for treating incompetent GSVs are not new. Duplex-guided sclerotherapy for treatment of GSV reflux has been attempted, but long-term studies have failed to prove durability comparable to surgery (15–19). Initial attempts at damaging vein walls by electrocoagulation involved creation of a thrombus within the vessel lumen, ultimately resulting in recanalization (20–22). Early methods of intraluminal delivery of high-frequency alternating-current radiofrequency (RF) energy to treat GSV reflux were complicated by skin burns, saphenous nerve and peroneal nerve injury, phlebitis, and wound infection (23).

A more modern technique of the use of RF energy to eliminate saphenous vein reflux has been developed by VNUS Medical Technologies (Sunnyvale, CA). Early results reported from a multicenter trial demonstrated a reasonable degree of success with an overall failure rate of 10% at a mean follow-up of 4.7 months (13% in patients treated with RF alone and 5% in patients treated with RF plus high ligation of the GSV). Complications included transient paresthesias (thigh, 9%; leg, 51%), skin burns (3%), deep venous thrombosis (3%), and one pulmonary embolus (24). More recent studies have demonstrated success rates of 73%–90% with follow-up to 24 months in 21 limbs (25–27).

One of the limitations of our study is that it does not provide a blinded, randomized comparison of the various modern percutaneous methods available for treatment of GSV reflux, including RF and wavelengths of laser energy other than 810 nm. However, review of the literature allows some comparisons and raises some interesting areas for future study.

RF current damages tissue by resistive heating of structures in direct con-

a. b.

Figure 3. Significant improvement in appearance of varicose tributaries after endovenous laser treatment of an incompetent left GSV. (a) Typical appearance of varicose veins caused by GSV reflux; (b) the same leg 1 month after endovenous laser treatment.

tact with the electrodes. Deeper tissue planes are heated by conduction into normothermic tissue. Because the potential for heating of adjacent perivenous tissue is high, safe treatment with RF depends on proper delivery of adequate tumescent anesthesia. Effective use of tumescent anesthesia appears to have reduced the incidence of heat-related complications. In expert hands, the incidence of paresthesias after RF has occurred in as few as 8.5% of limbs within 1 week of treatment and decreased to 0.7% at 6 months (27). However, with less-experienced physicians, RF still has been complicated with heat-related adverse effects such as paresthesias (10% at 6 months) and skin burns (3.3%) (25).

Published experience with endovenous laser with use of wavelengths other than 810 nm is limited. A recent study by Chang and Chua (28) reported the use of 1,064-nm laser energy delivered endovenously for treatment of GSV reflux. Although this study reported a success rate of 96.8% in 244 legs followed up to 28 months, significant complications were noted, including paresthesias (36.5%) and skin burns (4.8%). In addition to endovenous laser ablation, all patients in their study underwent surgical ligation and division of the proximal and distal ends of the treated GSV. In addition, patients treated with the 1,064-nm wavelength underwent spinal or general anesthesia rather than strictly local tumescent anesthesia (28).

In comparison, in our series of more than 500 limbs treated with 810-nm diode laser energy delivered endovenously, there have been no heat-related complications despite the high temperatures attained at the laser fiber tip. This may be explained by the following: (1) improved delivery and use of sufficient amounts of tumescent fluid in the proper tissue plane providing a protective thermal "sink;" (2) selective, homogeneous, and circumferential heating of the inner vein wall by absorption of 810-nm laser energy by blood lining the vein wall, as noted in a recent study by Proebstle et al (29), rather than deeper penetration of laser energy and less-homogeneous heating from endovenous laser performed with wavelengths such as 1,064 nm, which are absorbed less by blood and more by water; and (3) faster rates of withdrawal and shallower depth of penetration of 810-nm laser energy, resulting in less damage to surrounding nontarget tissue compared with methods that use RF.

It has been suggested that a randomized controlled trial comparing outcomes of endovenous laser ablation of the saphenous vein to surgical ligation and stripping should be performed; however, such a study would be difficult given patients' overwhelming desire for minimally invasive treatments rather than surgery. Review of the existing surgical literature does provide some insight in assessing treatment durability. Multiple studies have shown that recurrence of varicose veins after GSV stripping occurs early (30), with 73% of limbs destined for recurrent varicosities at 5 years already having them at 1 year (31,32). Our results with endovenous laser have supported this, demonstrating that what is found on duplex imaging early is predictive of what will be seen later, with none of the treated patients developing recanalization of successfully occluded GSVs at 2 or 3 years that was not seen before 9 months.

Performing endovenous ablation of the GSV without dissection of the SFJ violates a cardinal rule in saphenous vein surgery that each of the tributaries must be individually divided. Surprisingly, the combined experiences with transcatheter endovenous ablation procedures have shown lower recurrence rates than with surgical ligation and stripping. Perhaps minimizing dissection in the groin and preserving venous drainage in normal, competent tributaries while removing only the abnormal refluxing segments does not incite neovascularization.

The understanding of venous disorders continues to improve with tremendous strides being made over the past decade. Readily available noninvasive diagnostic tests allow physicians to precisely map out abnormal venous pathways and identify sources of incompetence. Modern percutaneous methods of sealing incompetent veins

provide patients with alternatives to ligation and stripping for treatment of GSV reflux without the familiar morbidities associated with surgery (33,34). Given these recent advances, many physicians, when properly trained, will now be able to successfully diagnose and treat the whole spectrum of superficial venous insufficiency, offering acceptable options to the millions of people in the United States alone who have varicose veins but are unwilling or unable to undergo surgery.

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Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood

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BACKGROUND. Despite the clinical efficacy of endovenous laser treatment (EVLT), its mode of action is incompletely understood.

OBJECTIVE. To evaluate the role of intravascular blood for the effective transfer of thermal damage to the vein wall through absorption of laser energy.

METHODS. Laser energy (15 J/pulse, 940 nm) was endovenously administered to explanted greater saphenous vein (GSV) segments filled with blood ($n = 5$) or normal saline ($n = 5$) in addition to GSVs under in vivo conditions immediately prior to stripping. Histopathology was performed on serial sections to examine specific patterns of damage. Furthermore, in vitro generation of steam bubbles by different diode lasers (810, 940, and 980 nm) was examined in saline, plasma, and hemolytic blood.

RESULTS. In saline-filled veins, EVLT-induced vessel wall injury was confined to the site of direct laser impact. In contrast, blood-filled veins exhibited thermal damage in more remote areas including the vein wall opposite to the laser impact. Steam bubbles were generated in hemolytic blood by all three lasers, while no bubbles could be produced in normal saline or plasma.

CONCLUSION. Intravascular blood plays a key role for homogeneously distributed thermal damage of the inner vein wall during EVLT.

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RECENTLY, MINIMALLY invasive techniques have been clinically introduced for the effective treatment of varicose veins. In particular, VNUS closure[1,2] and endovenous laser treatment (EVLT)[3–5] have been shown to abolish reflux in the incompetent greater saphenous vein (GSV). Short-term efficacy has been reported as greater than 90%[1,2] and 95%,[3–5] respectively, comparing well with the results of classic surgery including high ligation and stripping of the GSV.[2] However, while the mode of action of VNUS closure has been studied in detail, the mechanisms of EVLT action are still not completely understood. It has been shown that EVLT, unlike VNUS, does not lead to occlusion of the vein by significant shrinkage of the vessel wall,[6] but instead causes a thrombotic occlusion of the laser-treated vein.[5]

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Histopathologic examination of laser-treated veins revealed perforation of the vein wall at the site of direct laser impact and thermal damage of adjacent vein wall areas.[5,6] For the latter effect, laser-induced steam bubble formation has been postulated as the responsible mechanism,[5] implicating a putative role for intravascular blood serving as a chromophore absorbing the laser energy. In order, to further clarify the role of intravascular blood during EVLT, we performed comparative in vitro and in vivo experiments in the presence or absence of intravascular blood.

Patients and Methods

Administration of Laser Energy to GSV Samples

EVLT was applied as previously described in detail.[5] In brief, a 600 μm bare fiber with an outer diameter of 1.00 mm was connected to a 940 nm diode laser. Under in vivo conditions (see Patients), the fiber was inserted below the knee into the surgically exposed GSV. The fiber was advanced proximally to the point of high ligation of the GSV and subsequently withdrawn in steps of about 3–5 mm while

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laser energy was applied.[5] Identical laser parameters were chosen for the in vitro experiments with GSVs (see below).

In Vitro Experiments With GSVs

After classic varicose vein surgery of the GSV under tumescent local anesthesia,[7,8] the stripped vein segment was transferred to a saline bath at room temperature. The veins were cut into pieces 10 cm in length, and each piece was ligated at the proximal end before the laser fiber was inserted from the distal end. The vein was then filled either with heparinized blood (500 IU heparin/20 ml of blood) or with normal saline. After the distal end was ligated tightly around the laser fiber, single laser pulses of 15 J (15 W, 1 second) were delivered every 3–5 mm during stepwise withdrawal of the fiber tip. During the entire procedure the vein was bathed completely in normal saline solution. A total of 10 specimens, 5 filled with blood and 5 filled with normal saline during treatment, were subsequently fixed in formaldehyde, embedded in 1 mm rings in paraffin blocks, and studied histologically in routine hematoxylin and eosin stains on serial 5 μm sections. Each section was evaluated with respect to signs of thermal damage at the site of direct laser impact, at the adjacent area, and at more distant sites. Particular attention was given to the vein wall opposing the site of direct laser impact.

Patients

Two patients scheduled for classic varicose vein surgery under tumescent local anesthesia[7] consented to undergo experimental EVLT in the interval between high ligation and stripping of the GSV. One patient received EVLT with a blood-filled GSV. In the second patient, conditions were identical, apart from the fact that blood was washed out of the GSV and replaced by normal saline prior to EVLT. Complete replacement of blood by saline solution was confirmed visually by a flexible vascular fiberscope. The time interval between EVLT and invaginated stripping was 15 minutes. The vein was then cut into 2 cm sections, fixed in formaldehyde, and embedded in paraffin blocks for later histologic examination.

Laser-Generated Steam Bubbles in Normal Saline, Plasma, or Hemolytic Blood

An in vitro setup to measure laser-generated steam bubble sizes was used as previously described.[5] Diode lasers with 810 nm, 940 nm, and 980 nm were used with appropriate 600 μm fibers as provided by the manufacturers. Before starting the comparative experiments, the energy output of each device was calibrated at the fiber tip with a power meter. Before each experiment, the fiber tips were freshly cut to avoid secondary carbonization effects. Each laser wavelength was tested in tubes filled with normal saline, human plasma, and hemolytic blood by administration of pulses between 3 and 16 J. Plasma was obtained by centrifugation of heparinized blood for 20 minutes at 2000 g. Hemolytic blood was produced by replacing the removed plasma with equal volumes of distilled water.

Results

EVLT was performed under in vitro conditions on GSV segments either filled with blood (n = 5) or filled with normal saline (n = 5). In addition, EVLT was performed in vivo after high ligation but before stripping of the GSV, in a vessel filled with either blood or normal saline. The generation of steam bubbles in normal saline, plasma, and hemolytic blood was examined for laser wavelengths of 810, 940, and 980 nm under in vitro conditions.

Pathologic Examination of GSV Segments Receiving In Vitro EVLT

A minimum of 20 hematoxylin and eosin-stained serial sections of each vein segment were examined microscopically. Detectable changes of the vein wall, attributable to endovenous laser action, were highly reproducible. Figure 1 displays representative cross sections of laser-treated GSV segments. In saline-filled veins, vein wall damage was exclusively confined to the site of direct laser impact (Figure 1B), while adjacent regions (Figure 1A) and, in particular, the opposite side of the vein wall (Figure 1C) show virtually no signs of tissue damage. In contrast, pronounced thermal damage was detectable along the entire vein wall in blood-filled veins (Figure 1D,E), even at the vein wall opposite the laser impact (Figure 1F).

Pathologic Examination of EVLT Effects on Surgically Removed Veins

The histopathologic examination of veins stripped after EVLT under in vivo conditions showed a similar pattern of thermal damage as the veins treated under in vitro conditions described above. Figure 2 displays representative sections of laser-generated complete perforations of the vein wall produced from the saline-filled (Figure 2A,B) or blood-filled (Figure 2D,E) vein. Again, the immediate site of laser impact exhibited a comparable extent of coagulative necrosis, regardless of whether the vein contained saline (Figure 2A) or blood (Figure 2D). However, even the immediately adjacent inner vein wall showed distinct differences in the extent of thermal damage (Figure 2A,B,D,E), with severe injury in the blood-filled vein and a virtually normal situation in the saline-filled vein. Also, the vein wall located at the opposite site of the laser impact showed heat damage in the blood-filled vein (Figure

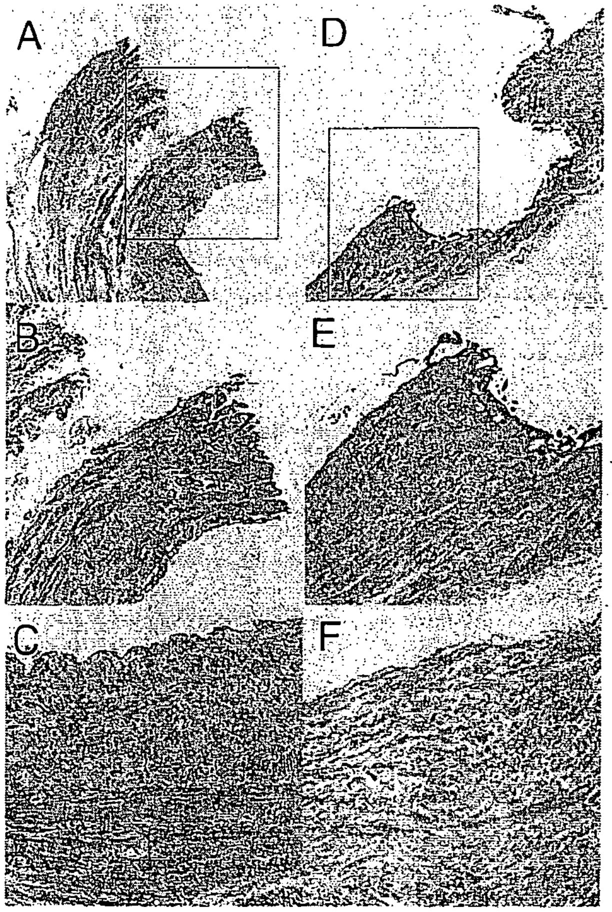

Figure 1. Representative hematoxylin and eosin sections of GSV segments after in vitro EVLT of A–C) saline filled veins or D–F) veins filled with heparinized blood. Under both conditions, direct laser impact causes perforation (A,B) or pronounced tissue ablation with focal coagulation necrosis at the immediate site of impact (D,E). In contrast to the saline-filled vein (A,B), the blood-filled vein exhibits more intensive and more remote injury to the adjacent vein wall areas (D,E). Likewise, superficial coagulative injury to endothelium, intima, and inner media are seen in vein wall areas on the opposite side of the laser impact in blood-filled veins (F), but are virtually absent in saline-filled veins (C). At most, slight tissue edema may be seen (C). Original magnification 55× (A,D) and 140× (B,C,E,F).

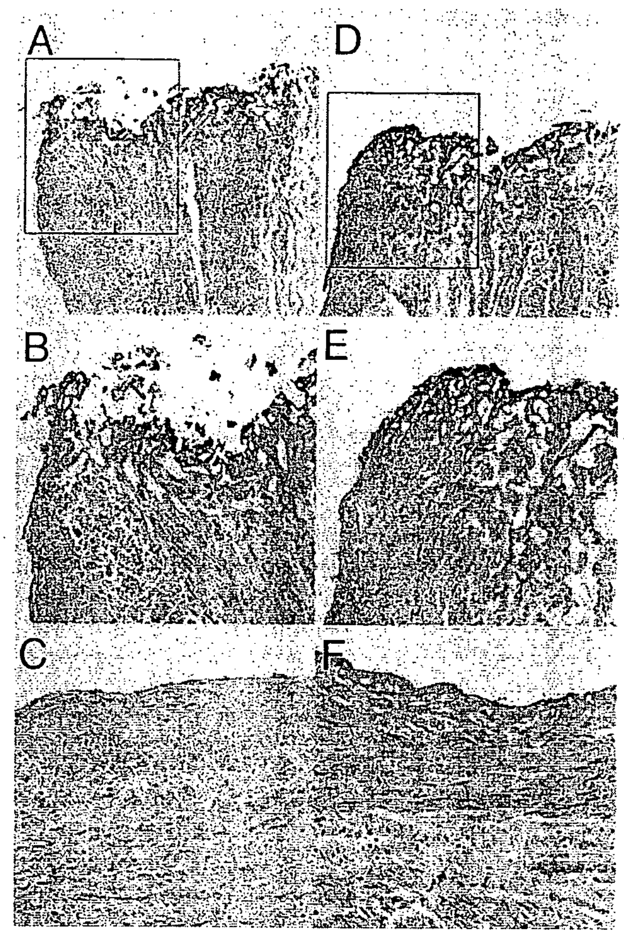

Figure 2. Histopathologic results of in vivo EVLT obtained from A–C) saline-filled or D–F) blood-filled veins. Arrangement of the panels as well as histomorphologic changes are identical to those described in Figure 1 and in the Results section of the manuscript.

2F), while in the saline-filled vein, only minimal laser-induced thermal damage was observed (Figure 2C).

Laser-Induced Steam Bubbles in Normal Saline, Plasma, and Hemolytic Blood

For laser wavelengths of 810, 940, and 980 nm, steam bubble volumes were plotted against the administered pulse energy (Figure 3). If the tube was filled with normal saline or plasma, no wavelength was able to produce detectable steam bubbles with pulse energies up to 16 J (data not shown). In contrast, in tubes filled with hemolytic blood, steam bubble sizes showed an almost linear proportionality with the administered laser energy. Note that no major difference could be detected between the three laser wavelengths. This indicates that the absorption of all three lasers by hemolytic blood is strong enough to transfer the energy completely into heat.

However, we found that this was true only if fresh-cut fiber tips were used for each experiment. Otherwise carbonization of the fiber tip led to extremely high tip temperatures, causing additional generation of energy through combustion of organic compounds of the hemolytic blood (data not shown).

Discussion

Despite growing acceptance and a rapid clinical introduction of EVLT, the underlying mechanism of action of this novel technique is still not fully understood. In a recent report of Weiss[6] it was demonstrated in elegant animal studies that endovenous radiofrequency

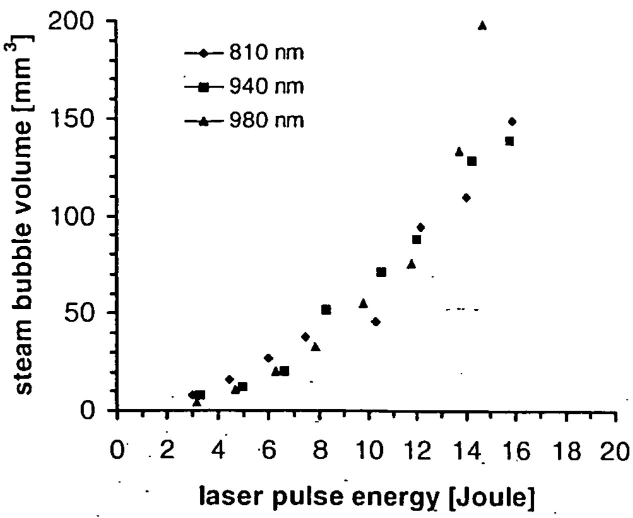

Figure 3. Laser-induced steam bubble volume in hemolytic blood plotted against delivered pulse energy for wavelengths of 810 nm (rhomboid), 940 nm (square), and 980 nm (triangle). No steam bubbles were produced with any of the experimental conditions in normal saline or plasma (data not displayed).

occlusion and EVLT have completely different modes of action. EVLT almost completely lacks the shrinkage effect of the vessels caused by prolonged exposure to moderate heat (85°C) in radiofrequency occlusion. Instead, EVLT causes perforation of the vein wall at the site of direct laser impact,[5,6] as a morphologic correlate for the consecutively observed perivenular ecchymoses.

In a previous report,[5] we proposed that laser-generated steam bubbles transfer a substantial amount of thermal damage to the vein wall during EVLT. These steam bubbles are created because of the high absorption of 940 nm laser energy in blood, with a technical penetration of only 0.3 mm. In water, this penetration depth is as much as 45 mm,[9] which is more than 100-fold deeper than in blood. Conversely, this implies that the absorption of 940 nm laser energy in water is less than 1% when compared to blood. Since under the particular topographic conditions of an endovascular laser fiber, a laser beam hits the vein wall within a markedly shorter distance than 45 mm, it can be concluded that heat generation by laser absorption cannot play a major role within a saline-filled vein. In this case, a laser beam of less than 1 mm diameter, with a fluence of more than 1500 J/cm^2, directly hits the vein wall, leading to complete perforating ablation of tissue (Figures 1A,B and 2A,B).

Our experimental setup tested this hypothesis under in vitro and in vivo conditions, providing histopathologic evidence: In a saline-filled vein almost the entire amount of focused laser energy is transferred to a small area at the vein wall, while in a blood-filled vein the thermal damage extends over a much wider topographic range of the inner vein wall, including the perilesional area and even areas opposite the immediate laser impact. This concordance between the in vitro and in vivo results suggests a sufficient correlation and validity of our in vitro model for the in vivo situation, despite the fact that under in vivo conditions the vein is much more compressed from outside by the presence of tumescent local anesthesia. However, one could speculate if a reduced, but still blood-filled, lumen of the vein could even facilitate laser-induced damage: relatively lower energies would suffice, because steam bubbles do not need to be generated in sizes that would be necessary to transfer homogenous damage to larger veins.

Evidence that blood plays not only a key role in absorption of 940 nm laser energy but also in absorption of 810 nm and 980 nm laser energy was provided by in vitro examination of steam bubble generation. While neither normal saline nor plasma were able to absorb laser energy substantially enough to generate steam bubbles, all three tested lasers produced comparable steam bubbles when exposed to hemolytic blood. Such steam bubbles, in all three laser systems, indicate that blood temperature passes the point of boiling at the site of the laser tip, thus transferring heat energy homogeneously to the inner vessel wall. The formation of these steam bubbles during EVLT could easily be monitored real time by duplex scanning, even allowing a continuous pullback of the laser fiber with the laser in continuous wave mode. One may speculate if with such a continuous pullback technique, perforations of the vein wall during EVLT could be avoided. However, a too-slow pullback velocity would certainly lead to a completely perforating longitudinal cut in the vein wall. Further experiments are needed on this topic. Therefore we hope that this improved knowledge about the exact mode of action of laser-induced vein damage may contribute to an improvement of endovenous laser treatment.

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Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: Thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles

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Purpose: Despite a rapid spread of the technique, very little is known about the laser-tissue interaction in endovenous laser treatment (EVLT). We evaluated EVLT of the incompetent greater saphenous vein (GSV) for efficacy, treatment-related adverse effects, and putative mechanisms of action.

Methods: Twenty-six patients with 31 limbs of clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R with incompetent GSV proven by means of duplex scanning were selected for EVLT in an outpatient setting. A 600-μm fiber was entered into the GSV via an 18-gauge needle below the knee and proceeded to the saphenofemoral junction (SFJ). After infiltration of tumescent local anesthesia, multiple laser pulses of 15 J energy and a wavelength of 940 nm were administered along the vein in a standardized fashion. D-dimers were determined in peripheral blood samples 30 minutes after completion of EVLT in 16 patients and on postoperative day 1 in 20 patients. One GSV that was surgically removed after EVLT was examined by means of histopathology. Additionally, an experimental in vitro set-up was constructed as a means of investigating the mechanism of laser action within a blood-filled tube.

Results: A median of 80 laser pulses (range, 22-116 laser pulses) were applied along the treated veins. On days 1, 7, and 28, all limbs except one (97%) showed a thrombotically occluded GSV. In one patient, the vessel showed incomplete occlusion. The distance of the proximal end of the thrombus to the SFJ was a median 1.1 cm (range, 0.2-5.9 cm) in the remaining patients. Adverse effects in all 26 patients were ecchymoses and palpable induration along the thrombotically occluded GSV that lasted for 2 to 3 weeks. In two limbs (6%), thrombophlebitis of a varicose tributary required oral treatment with diclofenac. D-dimers in peripheral blood were tested with normal results in 14 of 16 patients 30 minutes after completion of the procedure and elevated results in 7 of 20 patients at day 1 after EVLT. However, an increase of D-dimers from day 0 to day 1 was observed in 15 of the 16 patients undergoing tests 30 minutes after EVLT and on day 1. The 940-nm laser was demonstrated by means of in vitro experiments and the histopathological examination of one explanted GSV to act by means of indirect heat damage of the inner vein wall.

Conclusion: EVLT of the GSV with a 940-nm diode laser is effective in inducing thrombotic vessel occlusion and is associated with only minor adverse effects. Laser-induced indirect local heat injury of the inner vein wall by steam bubbles originating from boiling blood is proposed as the pathophysiological mechanism of action of EVLT. (J Vasc Surg 2002; 35:729-36.)

For many patients of clinical stages C_2 to C_6 with proven incompetence of the saphenofemoral junction (SFJ) and refluxes along the greater saphenous vein (GSV), the standard surgical treatment still is high ligation of the vessel and its tributaries at the level of the SFJ, with subsequent stripping of the incompetent part of the GSV. In the last decade, less-invasive techniques have been further developed, particularly the use of tumescent local anesthesia facilitated ambulatory phlebectomy[1,2] or high ligation and stripping of the GSV.[3-5] In the last few years, a radio-frequency heating technique has been developed as an endoluminal approach with a distal, microsurgical vein access producing excellent cosmetic results.[6] One distinct major difference compared with classic varicose vein surgery is that endoluminal radio-frequency solely occludes the GSV without affecting tributaries at the level of the SFJ. Such a strategy is particularly remarkable, because it is generally accepted that recurrent varicose veins after surgery often have their origin in residual tributaries of the SFJ or in a residual saphenous stump. A recent study that suggested that, at least with short-term follow-up, extended ligation at the SFJ did not add much when compared with endoluminal closure of the GSV alone[7] raised a very controversial discussion. More recently, a similar minimally invasive technique, endovenous laser treatment (EVLT) of the GSV has been introduced,[8] and, in contrast to transcutaneous laser treatment of reticular veins and venulectasias,[9,10] we are only starting to learn about the

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Competition of interest: Dr Rother, who constructed the experimental set-up for in-vitro testing, is an employee of Dornier MedizinLaser GmbH, Germering, Germany.

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Table I. Characteristics of 31 treated limbs of 26 patients who underwent endovenous laser treatment, according to the CEAP classification

	Number of limbs(%)
Clinical stage	
C2 Varicose veins > 4 mm	31 (100)
C3 Edema	25 (81)
C4 Skin changes	11 (35)
C5 Healed ulcer	0 (0)
C6 Active ulcer	4 (13)
Etiology	
Primary	31 (100)
Secondary	0 (0)
Anatomy	
Superficial veins	31 (100)
Perforator veins	17 (55)
Cockett II/III	14 (45)
Sherman	3 (10)
Deep veins	0 (0)
Pathology	
Reflux	31 (100)
Obstruction	0 (0)

efficacy, adverse effects, and mode of action of this novel approach.

This study was conducted to obtain more detailed clinical and histopathological data on the application of EVLT in patients with clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R, including an incompetent GSV. An in vitro set-up was developed and used as a means of further clarifying the ~~mode of action of EVLT on the inner vessel wall.~~

METHODS

Patients. Patients were selected from our phlebology clinic as they came in for evaluation of specific complaints. As part of their routine examination, all patients underwent functional testing, including duplex scanning (Sonosite 180 plus, 4med, Erlangen, Germany). When a clinical stage C_2 to C_6 with an incompetent SFJ and reflux in the GSV were revealed by means of the phlebological examination, and thus an indication for high ligation and stripping was presented, patients were asked to choose between classic varicose vein surgery or EVLT. Only three of 29 patients preferred classic varicose vein surgery, whereas 26 patients chose EVLT. However, patients made this decision after reading information and an additional personal discussion with the physician about EVLT, which, in contrast to surgery, so far has no long-term follow-up, and the possible need for additional treatment measures, including classic surgery, later. Apart from the incompetent GSV, other incompetent superficial veins and perforator veins were tolerated, but not treated simultaneously to EVLT. Patients with secondary varicosis with deep vein reflux or deep vein obstruction were not able to undergo EVLT (Table I). All patients gave written informed consent in accordance to the Helsinki declaration.

Administration of laser energy. The whole EVLT procedure was exclusively limited to the GSV, and no additional measures like mini-phlebectomy or sclerotherapy were used as a means of treating tributaries of the GSV simultaneously. Roughly, the protocol was adapted from the paper of Navarro et al.[8] After duplex scanning-guided puncture of the GSV below the knee with an 18-gauge venous catheter (Vasofix, Braun, Melsungen, Germany), a J-tip guidewire (0.035-in, Medex Medical, Rossendale, UK) was advanced by means of duplex scanning control toward the SFJ. A 5F angio catheter (Infiniti, 100 cm, 0.97 mm, vertebral, Cordis Europe, 9301 LJ Roden, Netherlands) was shortened at the tip with a scalpel by approximately 5 cm to allow passage of the bare fiber more easily. The catheter was then forwarded over the guidewire until its tip was located approximately 1 cm distal to the SFJ. The guidewire was then removed and replaced by a 600-µm bare fiber with an outer diameter of 1.00 mm (Type D-6100-BF, Dornier MedizinLaser GmbH, Germering, Germany) connected to a 940-nm diode laser (Medilas D, Dornier MedizinLaser GmbH). With duplex scanning control, the laser fiber tip was passed through the tip of the angio catheter, thus extruding approximately 6 to 8 mm, with a final distance toward the SFJ of 1 to 2 cm. The correct location of the fiber tip could also be verified visually: in the darkened operation theater, the red (645 nm, 1 mW) pilot beam was detectable transcutaneously. Tumescent local anesthesia was then infiltrated along the GSV from the SFJ down to the point of access, as described elsewhere,[3] and given 5 minutes to establish the anesthetic effect before the start of the laser treatment. Laser energy was delivered in a pulsed fashion with a 1-second on and a ~~2-second off period. During the on period, 15 J of laser~~ energy were delivered with a power of 15 W. During the off period, the fiber tip was retracted 5 to 7 mm. This cycle was repeated until a distance of 1 cm to the puncture site of the GSV was reached. In this manner, the laser treatment of the entire GSV lasted 3 to 5 minutes. Subsequently, the catheter was removed, and the patient received a full thigh class II compression stocking, resembling an ankle pressure of 30 mm Hg, and was advised to walk immediately. Additionally, as a precaution without any further rationale, low-molecular-weight heparin was administered subcutaneously for 5 days for thrombosis prophylaxis (Fragmin P, Pharmacia & Upjohn, Erlangen, Germany).

Concomitant duplex ultrasound scanning examination. All patients underwent duplex ultrasound scanning examinations before EVLT, during EVLT, and after EVLT on days 1, 7, and 28. During the course of the examinations, patients underwent scanning for refluxes in superficial veins, in the deep vein system, and also in perforating veins. Patients with an incompetent or occluded deep vein system were excluded from EVLT. Concomitant incompetent perforator veins or pathological findings in the superficial vein system were recorded, but did not prevent patients from receiving EVLT if the GSV was open and incompetent from the SFJ down to below the knee.

During EVLT itself, duplex scanning was particularly helpful in identifying the GSV at the puncture site, when necessary after full length down-scanning of the GSV from

the groin or up from the ankle. Duplex scanning was further an important means of localizing the precise position of the laser tip close to the SFJ before administration of tumescent local anesthesia, because afterward, because of the massive subcutaneous fluids, recognition of anatomical structures was almost impossible.

With scheduled duplex ultrasound scanning control examinations on days 1, 7, and 28, a full-length scanning of the treated vein was included as a means of demonstrating homogeneous thrombotic occlusion. Occlusive thrombosis was supposed when the vein was completely filled by an incompressible hypoechogenic mass and when no fluxes were detected within the vessel lumen. Similarly, in the region of the SFJ, the proximal ending of the thrombus was determined by means of compression and detection of fluxes. The distance of the proximal thrombus ending toward the junction with the deep femoral vein was measured. At day 28, the hypoechogenicity of the thrombus had almost disappeared. However, the lack of fluxes and the remaining incompressible vessel still allowed sufficient conclusions. Additional scanning of the deep vein system excluded a thrombotic affection there.

Testing for D-dimers in peripheral blood. After detection of EVLT-induced thrombotic occlusion, rather than an immediate closure of the GSV, we scheduled D-dimer testing for every patient. With the exception of the first six patients, D-dimer values (Tinaquant D-dimer, Roche Diagnostics, Mannheim, Germany) were scheduled to be determined from blood samples obtained 30 minutes and 1 day after the EVLT procedure. According to the manufacturer's data sheet, D-dimer values below 0.50 mg/L were considered to be within normal limits. However, because of technical reasons, blood sampling failed in four patients 30 minutes after EVLT.

Histopathologic examination. One patient gave informed consent to undergo EVLT as part of his routine varicose vein surgery procedure, which included extended high ligation of the SFJ and subsequent stripping of the incompetent parts of the GSV. EVLT was administered immediately after completion of extended high ligation, but before stripping of the GSV. The treated vein was left in place for another 15 minutes and then removed by means of stripping. The removed vein was photodocumented (Fig 1, *A*) and histopathologically examined with hematoxylin and eosin staining.

Mechanism of laser action. As a means of evaluating the mechanism of action of the 940-nm laser beam within the vein, an experimental set-up was designed (Fig 3, *A*). A silicone tube with an inner diameter of 6 mm was connected to a transparent tube with an inner diameter of 2 mm. The tube system was then filled with heparinized blood. From the opposite side, the laser fiber was inserted into the middle of the silicone tube. Different amounts of laser energy were then applied by means of variation of either laser power or pulse duration. With each laser pulse, the extension of the volume within the system was assessed by documenting the change in the blood level within the 2-mm tube. A cylindrical volume calculates as $V = h \times \pi r^2$ (eg, if a laser pulse produces a movement of the blood level of $h = 54$ mm, the laser generated steam volume calculates as $V = 54 \text{ mm} \times \pi[1 \text{ mm}]^2 = 170 \text{ mm}^3$, corresponding to a steam bubble length of 6 mm in a tube with a diameter of 6 mm). The temperature of the steam bubble is supposed to be close to 100° C and, once generated, should stay on this level constantly throughout its increase of volume, as it is known in the physics of phase transitions.

RESULTS

Twenty-six patients, 21 with unilateral and 5 with bilateral incompetent GSV, received EVLT by means of a 940-nm diode laser with tumescent local anesthesia. Nineteen patients were women (73%), and seven patients were men (27%), with 22 and 9 limbs treated, respectively. The median age of the patients was 57 years (range, 27-83 years). Before treatment, the median diameter of the GSV was 6.0 mm (range, 4.0-9.9 mm) at the level of the SFJ. In our relatively small cohort with a spectrum of clinical stages (Table I), the GSV diameter did not correlate with the body mass index of the patient (data not shown), the median of which was 26.6 (range, 20.0-39.7). The median amount of infiltrated tumescent local anesthesia was 650 mL per limb (range, 250-1000 mL).

Technical skills. Initially, before the use of duplex scanning for guided puncture of the GSV, access to the GSV failed in two of seven patients. These two patients underwent subsequent classic surgery. In four additional cases, insertion of the guidewire from below the knee to the SFJ was not possible in one step because of pronounced tortuosity of the GSV. In three of these four cases, an additional puncture of the GSV approximately 15 cm above the knee allowed treatment in two parts. In one case, EVLT was limited to the proximal 20 cm of the GSV because of the technical inability to obtain access to the more distal part of the GSV.

However, in all cases, duplex scanning-controlled placement of the fiber tip was achieved within a distance of 1 to 2 cm distal from the SFJ. In patients who were not overtly obese, this position could be visualized by means of transcutaneous illumination of the pilot laser beam. In our series of 31 limbs in 26 patients, this was true in four limbs of three male patients with a body mass index between 31.5 and 39.7. However, even in those obese patients, transcutaneous detection of the laser pilot beam was possible after applying gentle pressure to the overlaying skin.

Effects of endovenous laser treatment. During step-wise removal of the laser fiber, a median of 80 pulses (range, 22-116) of 15 J energy each were delivered, corresponding to a distance of 5 to 7 mm between laser pulses.

On days 1, 7, and 28 after treatment, thrombotic occlusion of the GSV was noted in all cases. In 30 of 31 limbs (97%), the thrombotic occlusion was complete from the distal puncture site, reaching proximally up to a median distance of 1.1 cm (range, 0.2-5.9 cm) from the SFJ. In one limb, the proximal occlusion of the GSV failed over a length of 20 cm despite complete occlusion of more distal parts of the GSV. The diameter of the GSV at the SFJ was 9.9 mm

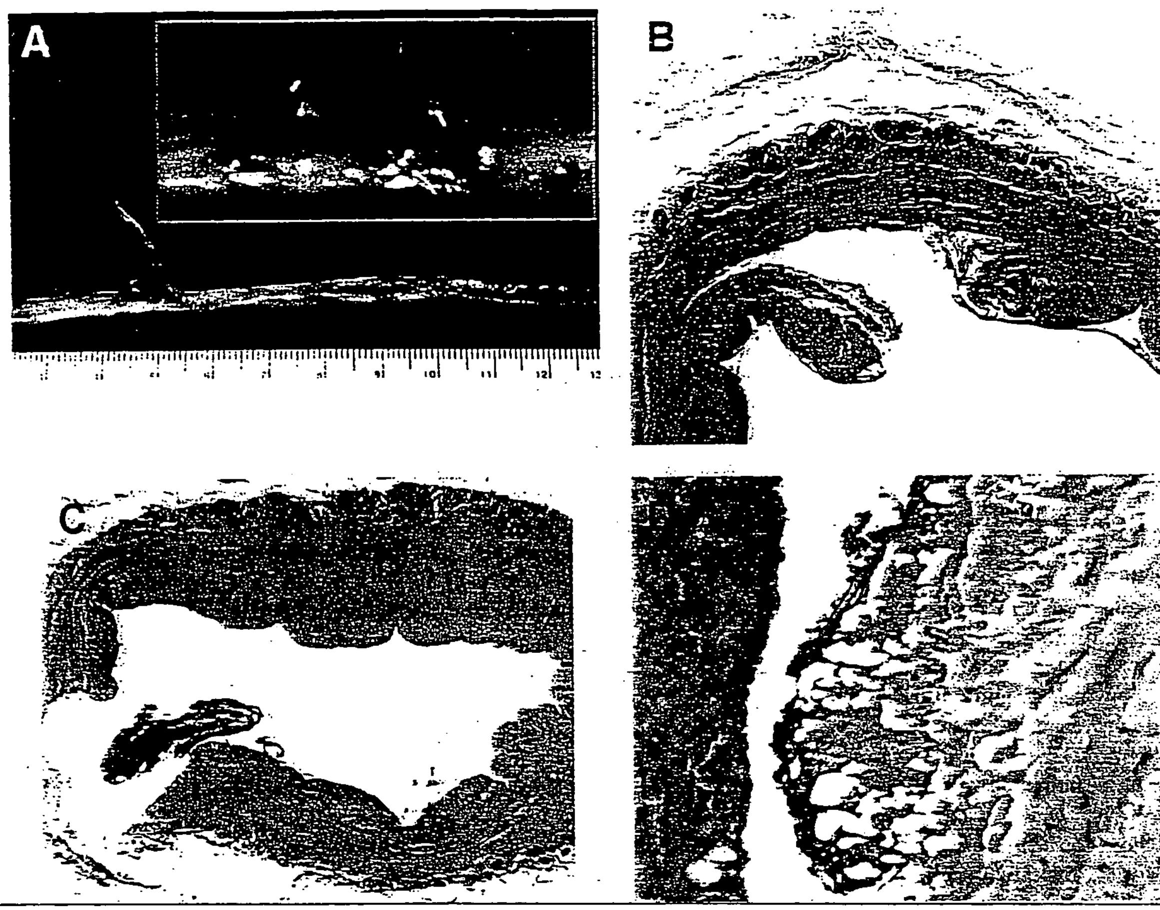

Fig 1. Macroscopic and microscopic hematoxylin and eosin-stained histopathologic examination of a GSV that has undergone EVLT before stripping. A, Outer surface of the endovenously laser-treated GSV. Dark spots resembling carbonization, or even full perforation of the vein wall, were caused by direct impact of the 940-nm laser beam. B, Intimal tear next to a non-perforating laser hit. C, Vein wall disruption caused by direct laser impact. D, High magnification of the margin area of vein wall disruption showing pronounced thermal damage, including carbonization.

and, therefore, the largest diameter of the whole series. Additionally, in this patient, we found by means of duplex scanning control a large caliber tributary with high blood flow feeding the GSV at the distal open point.

Adverse effects. After the local anesthetic effect subsided after EVLT, slight to moderate local pain was reported by all patients over the treated vein. Also, moderate ecchymoses, most likely caused by laser-induced perforation of the vein wall, could be observed in every patient at the inner thigh and knee region from the next day to approximately 2 weeks later. However, these ecchymoses were not as pronounced as they are usually with classic varicose vein surgery, and no hematoma was found. For the first 2 to 3 weeks after EVLT, also a slightly shorter period than frequently observed with classic surgical procedures, an induration was palpable along the treated GSV, and this was experienced by the patients as slight to moderate pain during extended movement of the leg. A thrombophlebitic reaction developed within an untreated varicose tributary at the distal thigh in two patients 2 and 5 days after EVLT. Oral treatment with diclofenac (75 mg, slow release, three times a day) resulted in immediate pain control. Hyperpigmentation developed in one patient over the thrombotically occluded GSV, which was still visible at 4 weeks after EVLT. All other patients were free of adverse effects at 4 weeks after the procedure. No other adverse effects or complications were reported.

D-dimers in peripheral blood. In 16 patients, D-dimer levels in peripheral blood were evaluated immediately after EVLT, and in 20 patients, blood samples were drawn on day 1 after EVLT (Table II). D-dimer levels were tested with normal results in all samples except one obtained 30 minutes after EVLT, with a median value of 0.39 mg/L (range, 0.09-0.80 mg/L). When D-dimer levels were tested at day 1 after EVLT in 20 patients, a median of 0.43 mg/L (range, 0.24-1.73 mg/L) was found. However, only seven blood samples showed D-dimer levels exceeding the upper limit of 0.50 mg/L. Although the

Table II. D-dimer levels in peripheral blood of patients who underwent endovenous laser treatment

	30 minutes after EVLT	*1 day after EVLT*	*Ratio 1 day/30 min*
Patients with1 limb treated	Median 0.30 mg/L (range 0.09-0.80) n = 13	Median 0.33 mg/L (range 0.24-1.73) n = 16	Median 1.39 (range 0.88-3.67) n = 13
Patients with 2 limbs treated	Median 0.45 mg/L (range 0.44-0.48) n = 3	Median 0.68 mg/L (range 0.50-0.91) n = 4	Median 1.82 (range 1.15-2.02) n = 3
All patients	Median 0.39 mg/L (range 0.09-0.80) n = 16	Median 0.43 mg/L (range 0.24-1.73) n = 20	Median 1.43 (range 0.88-3.67) n = 16

EVLT, Endovenous laser treatment.

absolute values remained mostly within normal limits, D-dimer levels were shown by means of intraindividual evaluation to increase from day 0 to day 1 in 15 of 16 patients who underwent both tests. The median increase ratio was 1.43 (range, 0.88-3.67), reflecting the process of thrombotic occlusion of the GSV. When separating the patients who received unilateral EVLT from patients who had a bilateral procedure (Table II), it looks as if patients with both limbs treated did not present the very low D-dimer values that are occasionally observed in patients with one limb treated. This observation might relate to two thrombotic processes instead of one, but also might be influenced by the thrombotic process having proceeded somewhat more in the first limb of those patients with bilateral EVLT. Unfortunately, the numbers are small in Table II and therefore do not warrant statistical analysis.

Pathologic examination of the endovenous laser treatment stripped vein. Macroscopically, the vein wall showed reddening, carbonization, or even perforation at those sites where the fiber tip was closest to the vein wall during delivery of laser energy (Fig 1, *A*). Either gross vein wall destruction associated with direct impact of the laser beam (Fig 1, *B-D*) or less pronounced heat-mediated vein wall injury (Fig 2, *B*, *C*) was demonstrated by means of microscopical examination of corresponding hematoxylin and eosin-stained slides. The heat injury demonstrated in Fig 2, *B* and *C*, was consistently detectable along the distance of 5 to 7 mm of vein wall, between the direct impact of two laser impulses, and is, in our opinion, the basis of a subsequent homogeneous thrombotic occlusion of the vessel. At those sites of direct laser action, the most destructive patterns of tissue damage can be observed: perforating and non-perforating vaporization of the vein wall, carbonization of the adjacent tissue margins, and intimal tear in response to the explosion-like delivery of high energy densities, called photo-disruption. However, because a stripping was performed after EVLT, some of the destruction observed, like intimal tears, may originate from the stripping procedure itself.

Mechanism of action of the 940-nm diode laser. Administration of different amounts of laser energy in the in vitro set-up was used as a means of evaluating the putative mechanism of laser action within the vein (Fig 3). During the experiments with heparinized blood in a silicone tube, we observed that a steam bubble formed during delivery of laser energy, and it collapsed immediately after discontinuation of the laser pulse. When we plotted the maximum volume of the laser-generated steam bubble against the amount of laser energy delivered, it showed a linear correlation (Fig 3, *C*). As calculated in the Methods section, a typical laser pulse with an energy of 15 J produced a steam bubble of approximately 6 mm in a 6-mm diameter vessel. As shown in Fig 3, *C*, the formation of a steam bubble required a threshold energy of about 1.5 J. This threshold energy is needed to heat up the surrounding blood until it reaches boiling temperature. A laser pulse energy below this level would only heat the blood, without any steam bubble formation.

DISCUSSION

The principal finding in this study is that EVLT with a 940-nm diode laser system, when performed under tumescent local anesthesia, is a clinically feasible and well-tolerated technique. Because of vein access via an 18-gauge needle, it is a truly minimal invasive procedure, leaving a virtually invisible scar on the patient's skin.

The efficacy of EVLT in obtaining early occlusion of the GSV is very satisfactory. Even if these are very early results, immediate closure rates of 97% in our series and 100% reported by another group with the 810-nm diode laser[8] provide a rationale for further evaluating this new method.

A major emphasis of this study was placed on the mode of action of this novel technique: technically, the depth of penetration of a 940-nm laser beam into blood is only approximately 0.3 mm.[11] Also, the laser beam remains focused to a very small spot after leaving the fiber tip. Although these characteristics of the laser beam could explain a focal perforation of the vein wall (Fig 1, *C*, *D*) immediately adjacent to the fiber tip, this would not adequately explain the widespread injury to the vein wall observed in the vicinity of the perforation sites (Fig 2, *B*, *C*). With our in vitro set-up, we could identify steam bubble formation at the laser tip (Fig 3, *B*). The volume of the laser-generated steam bubble correlated directly to the laser energy (Fig 3, *C*). Because such a

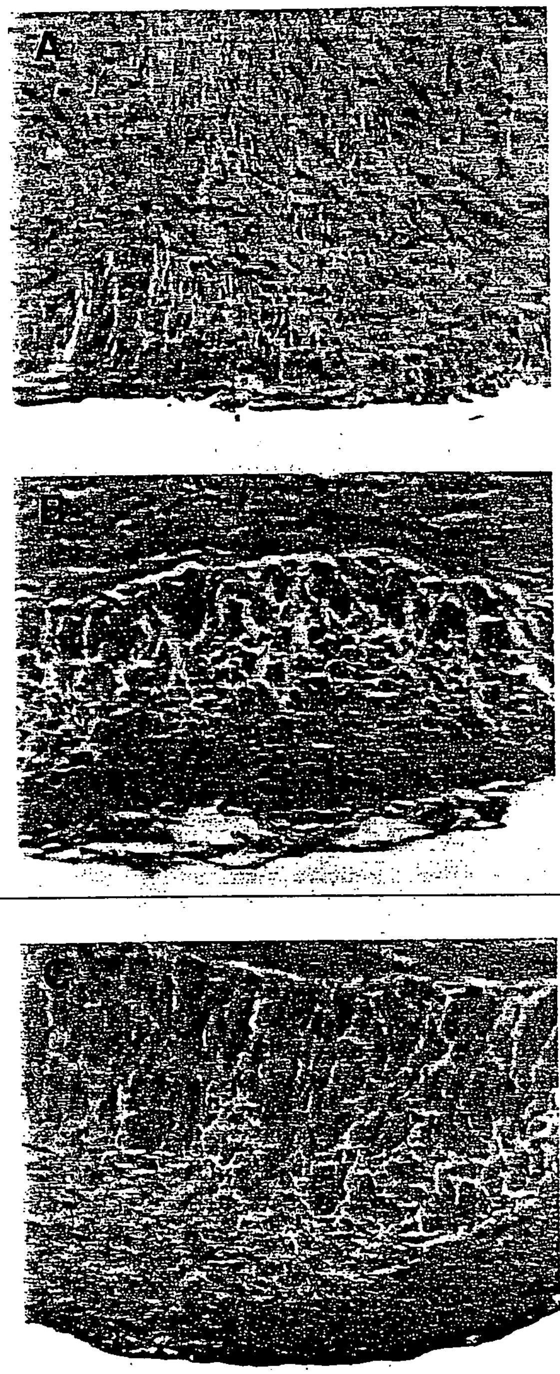

Fig 2. Indirect, steam bubble-mediated thermal damage after EVLT, several millimeters away from areas of direct laser impact. A, Control: normal varicose vein after stripping without earlier EVLT, with intact endothelium and distinct cellular contours. The nuclei are round to oval. B, EVLT resulted in a lift-off of endothelial cells, a denudation of the intima, loss of cellular contours, and fibrin deposition. Additionally, some areas show marked vacuolization of cells or even spongiosis. C, Swelling and waxy homogenization of collagen. Focal coagulation necrosis within the intima.

steam bubble formation is expected to occur within the vein lumen during EVLT, we propose that this phenomenon accounts for the thermal injury to an extended surface of the inner vein wall.

In a recent paper, Sadick et al[10] reported histopathological alterations of reticular veins and venulectasias after transcutaneous neodymium/yttrium-aluminum-garnet laser treatment that compare well with our findings. This opens the question of whether also in transcutaneous laser treatment of smaller veins the crucial damage of the vein may involve a similar steam bubble-mediated, hence indirect, thermal injury, rather than the immediate highly focused damage by the laser beam itself.

Steam bubble formation is a local, instantaneously reversible phenomenon that, after collapse of the bubble, poses no risk, such as gas embolism, to the patient. However, the extensive heat damage of the endothelium and the intima does induce the desired effect: full-length thrombotic occlusion of the vein. The complete thrombotic occlusion, however, is not detectable immediately after EVLT, but can be recognized at day 1 by means of a simple duplex scanning examination, which shows an incompressible, hypoechogenic cord in the lumen of the saphenous vein. This thrombotic occlusion is also reflected in all patients with an increase of D-dimer levels in peripheral blood by a median factor of 1.43. Because in our study and another study[8] no EVLT-induced deep vein thrombosis occurred, it seems very unlikely that the EVLT-induced thrombotic process of the GSV has a concomitant risk for deep vein thrombosis, as is known for superficial thrombophlebitis.[12] However, it remains unclear whether such an hypothetical risk of deep vein thrombosis does indeed exist or whether it is only so much lower compared with superficial thrombophlebitis[12] that it can only be detected in a larger series of patients.

Other commonly observed adverse effects with EVLT are induration along the GSV and mild-to-moderate ecchymoses. These ecchymoses, present for approximately 2 weeks, could be a cosmetic problem for patients who are expecting a minimally invasive, barely invisible treatment of their GSV incompetence. In this respect, EVLT would compare unfavorably with endoluminal radio-frequency closure. However, when weighed against the potential nerve damage after endoluminal radio-frequency treatment with subsequent skin paresthesis in as many as 16% of patients,[7] such an entirely reversible adverse effect seems quite acceptable.

Less frequent adverse effects, like thrombophlebitis of untreated tributaries or appearance of hyperpigmentation along the GSV, need to be followed and documented as the number of patients and EVLT procedures increase. At least the risk of thrombophlebitis could be avoided completely if varicose tributaries, unlike in the present series, are treated in the same session (eg, with mini-phlebectomy).[12]

Finally, it remains to be established whether EVLT induces effective long-term occlusion of the treated veins. Recurrent reflux, either originating from the SFJ or reoc-

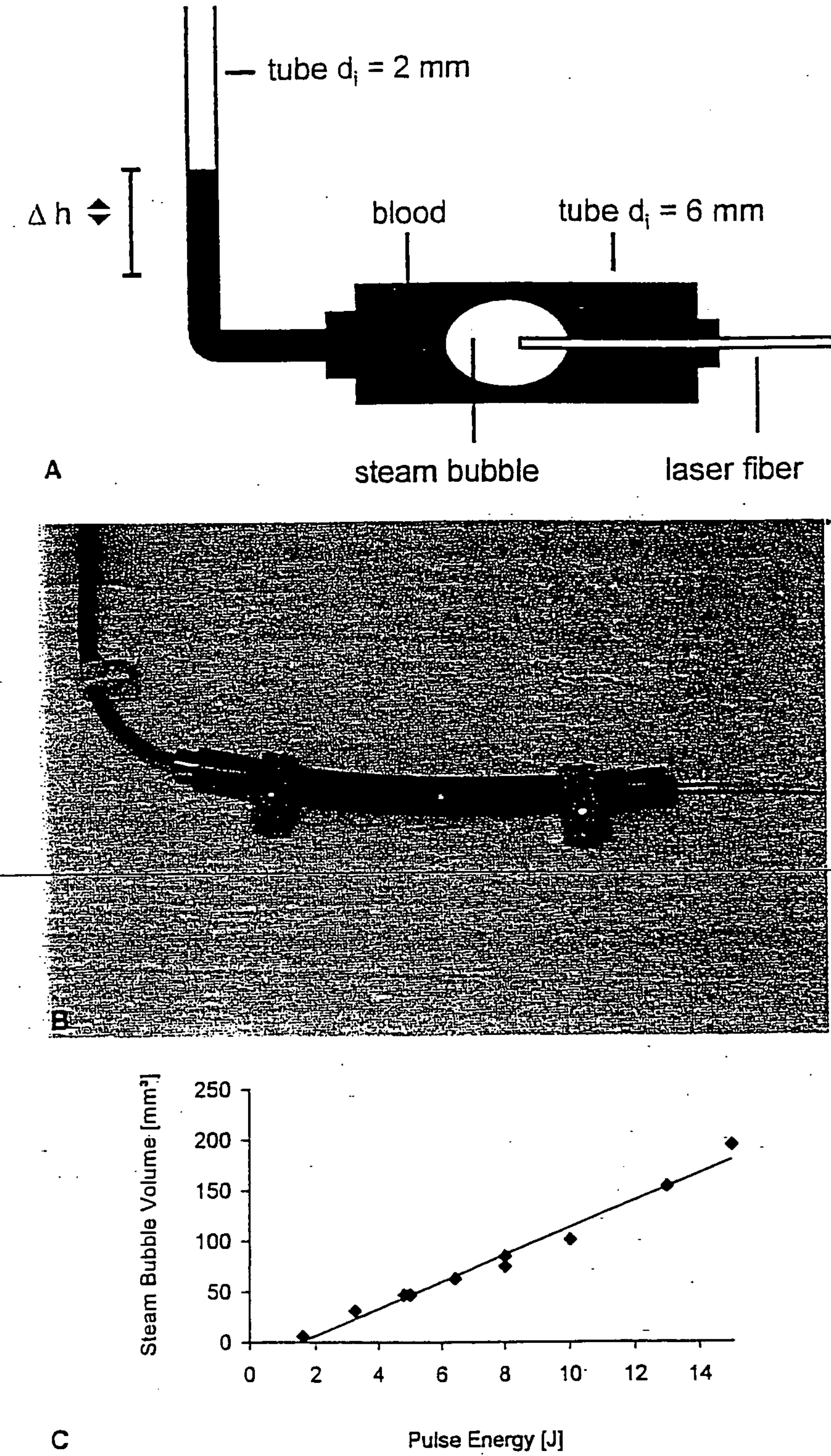

Fig 3. A, Schematic drawing of the in-vitro set-up for examining the laser-generated steam bubble formation. The laser fiber was inserted into a silicone tube of 6-mm-diameter filled with heparinized blood. During delivery of laser energy, heating and boiling of the blood finally lead to the formation of a steam bubble, pushing the corresponding blood volume out of the tube. Thus, the movement of the blood level in the smaller 2-mm-diameter tube allowed the calculation of the volume of the steam bubble in reverse. B, Visible steam bubble formation during delivery of a laser pulse of 15 J. C, Dependency of the steam bubble volume for various amounts of energy delivered by the laser beam.

curring within recanalized parts of the GSV, has to be followed closely. Only long-term follow-up in prospective trials will be able to answer this question.

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